SECTION 1 SCIENTIFIC ABSTRACT

Prostate cancer kills approximately 40,000 men annually. Although conventional therapies for prostate cancer produce a high rate of cure for patients with early stage disease, a significant fraction of these cancers recur and each therapy results in high morbidity. The prognosis for androgen-independent prostate cancer is much worse, as there is no effective treatment and a vast majority of these patients eventually succumb to the disease. There is a real need to develop new therapies that would reduce the morbidity associated with conventional therapies, decrease the incidence of tumor recurrence, and improve the outlook for recurrent and androgen-independent cancer.

Up to 80% of prostate cancer patients who receive radiation therapy as their primary treatment will fail biochemically (develop a rising PSA) within 5 years. Unfortunately, limited therapeutic options exist for such patients. Further external beam radiation is not an option because of radiation-induced complications. Cytotoxic chemotherapy is not curative and is typically reserved for palliation with symptomatic progression or asymptomatic patients with significant biochemical progression following hormonal therapy. Of the four remaining therapeutic options, including salvage radical prostatectomy, salvage RT with interstitial implants, salvage cryoablation of the prostate, and androgen deprivation, none has demonstrated a high degree of efficacy in eradicating tumor with a reasonable degree of safety. The ten year overall survival rate of patients with locally recurrent prostate cancer is only 35% as the disease invariably progresses to hormone-refractory metastases.

The scientific rationale for this phase I trial derives from research conducted in Drs. Kim's and Freytag's laboratories during the past 5 years. Our research program has developed a novel, trimodal gene therapy approach for the treatment of prostate cancer. An E1B-attenuated, replication-competent adenovirus (Ad5-CD/TK*rep*) is used to selectively and efficiently deliver a cytosine deaminase (CD)/herpes simplex virus thymidine kinase (HSV-1 TK) fusion gene to tumors. Preclinical studies in animals have demonstrated that the Ad5-CD/TK*rep* virus itself generates a potent anti-tumor effect by replicating in and preferentially destroying human prostate cancer cells. The therapeutic effect of the Ad5-CD/TK*rep* virus can be significantly enhanced by invoking two suicide gene systems (CD/5-FC and HSV-1 TK/GCV), which render malignant cells sensitive to specific pharmacological agents and sensitizes them to radiation.

In this phase I trial, the toxicity and efficacy of two arms of our trimodal approach will be evaluated in patients with local recurrence of prostate cancer following radiation therapy. Locally recurrent tumors will be injected with the Ad5-CD/TK*rep* virus under transrectal ultrasound guidance. The protocol calls for an escalating viral dose trial beginning at 1×10^{10} viral particles (vp) in four patients. Two days after viral administration, patients will receive oral administration of 5-FC (150 mg/kg/day) and intravenous infusion of GCV (5 mg/kg/dose) for seven days. If there are no serious adverse side effects, the viral dose will be escalated to 1×10^{11} vp and then 1×10^{12} vp in subsequent groups of four patients. A total of 12 patients will be enrolled. Effectiveness will be monitored by serial measurements of serum prostate specific

antigen (PSA), digital rectal examination (DRE), transrectal ultrasound (TRUS) of the prostate, and prostate biopsy. The primary aim of this initial study is to determine whether Ad5-CD/TK*rep* viral therapy concomitant with double prodrug therapy is associated with significant toxicity. Based on an accrual rate of one patient per month, this phase I study should be completed in 12 months.